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L16: Entry 24 of 39 File: USPT Oct 5, 1999

DOCUMENT-IDENTIFIER: US 5962323 A
TITLE: Expansion of bone marrow stromal cells

Brief Summary Paragraph Right (6):
Bone marrow transplantation or implantation is a promising therapy for a number of diseases that involve hematopoietic cells. Transplantation can serve to replace cells that have been damaged by an intrinsic disease, such as an anemia, or in instances where hematopoietic cells have been destroyed by chemotherapy or radiation therapy. Transplantations can be autologous, i.e., the patient can serve as his or her own donor. Alternatively, a patient could receive bone marrow from a histocompatible donor. To date, however, conditions for culturing bone marrow, particularly bone marrow stromal cells, which could be transplanted and used in numerous gene therapies, have not been optimized. A major obstacle to gene therapies that are based on the modification of stromal cells is the procurement of therapeutically useful numbers of stromal cells. Consequently, despite the success of bone marrow transplantation, gene therapies that require successful transplantation of bone marrow stromal cells have not yet been realized.

Brief Summary Paragraph Right (7):
The invention is a novel method for culturing bone marrow stromal cells, and is based on the discovery that acidic FGF (aFGF), or a combination of aFGF and heparin, significantly enhances the establishment and subsequent expansion of bone marrow stromal cells. By employing this method, bone marrow stromal cells can be expanded in culture to previously unprecedented levels that are clearly beneficial for therapeutic uses. Thus, this culturing method allows bone marrow stromal cells to be used in many types of gene therapies.

Detailed Description Paragraph Right (1):
To develop cultures of bone marrow stromal cells that can be used for transplantation, bone marrow was obtained from humans or dogs and grown in specially prepared tissue culture flasks. In addition, the medium was modified with acidic fibroblast growth factor (aFGF) and heparin and was renewed according to a particular regimen. Using this novel method, a large number of bone marrow stromal cells were established in culture and expanded to yield an unprecedented number of cells, which would be required for effective gene therapy with stromal cells.

Detailed Description Paragraph Right (12):
This method can be used to select and expand canine or human (or other vertebrate) bone marrow stromal cells, to develop a total cell number of more than 10.sup.8, and even more than 3.times.10.sup.9 in vitro, from bone aspirates of individual subjects. Other techniques for obtaining bone marrow can also be used. The bone marrow stromal cells obtained from dogs by this method exhibit the characteristic appearance of fibroblast-like bone marrow stromal cells. Given that the success of gene therapy depends on the cellular production of adequate levels of the transgene product, which can be quite low, the ability to expand stromal cells in culture to 10.sup.8 to 10.sup.9 or more represents a substantial improvement.

Detailed Description Paragraph Right (25):
To determine whether bone marrow stomal cells that were grown according to the methods described above could be transfected, the plasmid expression vector pETKhGH was prepared and transfected into canine stromal cells using standard techniques. The dog model is an accepted animal model of the human bone marrow system, and

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L16: Entry 24 of 39 File: USPT Oct 5, 1999

US-PAT-NO: 5962323
DOCUMENT-IDENTIFIER: US 5962323 A

TITLE: Expansion of bone marrow stromal cells

DATE-ISSUED: October 5, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Greenberger; Joel S.	Sewickley	PA		
Hurwitz; David R.	Acton	MA		

US-CL-CURRENT: 435/384; 435/350, 435/372, 435/378, 435/395, 435/405, 530/350, 536/21

CLAIMS:

What is claimed is:

1. A method for the expansion of bone marrow stromal cells, the method comprising:

(a) introducing bone marrow stromal cells into a vessel containing a culture medium comprising an acidic fibroblast growth factor ("aFGF") polypeptide; and

(b) expanding the stromal cells in the culture medium under conditions and for a time sufficient to obtain an increased number of bone marrow stromal cells.

2. The method of claim 1, wherein the culture medium further comprises at least 0.05 units/ml heparin.

3. The method of claim 2, wherein the culture medium comprises 1.0 to 50.0 percent by volume fetal bovine serum, 0.01 to 100.0 ng/ml aFGF polypeptide, and 0.05 to 100 units/ml heparin.

4. The method of claim 3, wherein the culture medium comprises 16.0 percent by volume fetal bovine serum, 1.0 ng/ml aFGF polypeptide, and 5.0 units/ml heparin.

5. The method of claim 1, wherein the expanding step (step (b)) comprises:

(i) removing culture medium and non-adherent cells from the vessel;

(ii) adding an amount of fresh culture medium to the vessel;

(iii) removing culture medium and non-adherent cells from the vessel and centrifuging the medium and non-adherent cells to form a pellet of non-adherent cells;

(iv) resuspending the pellet of non-adherent cells in an amount of culture medium taken from the vessel to form a non-adherent cell mixture; and

(v) returning the non-adherent cell mixture to the vessel.

6. The method of claim 5, wherein the amounts of fresh culture medium in step (ii)

and culture medium taken from the vessel to resuspend the pellet of non-adherent cells in step (iv) are equal.

7. The method of claim 6, wherein step (i) is performed after stromal cells have adhered to the inner surface of the vessel.

8. The method of claim 6, wherein steps (ii) and (iii) are performed about one week after step (i).

9. The method of claim 1, wherein the bone marrow stromal cells are fresh stromal cells obtained from primary aspirates of bone marrow from a vertebrate.

10. The method of claim 1, wherein the bone marrow stromal cells are obtained from bones removed from a vertebrate.

11. The method of claim 1, wherein the bone marrow stromal cells are obtained from a bone marrow stromal cell culture or from a frozen stock of bone marrow stromal cells.

12. The method of claim 1, wherein the bone marrow stromal cells are mammalian.

13. The method of claim 12, wherein the bone marrow stromal cells are human.

14. The method of claim 12, wherein the bone marrow stromal cells are canine.

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L16: Entry 29 of 39 File: USPT Sep 23, 1997

DOCUMENT-IDENTIFIER: US 5670351 A
TITLE: Methods and compositions for the ex vivo replication of human hematopoietic stem cells

Brief Summary Paragraph Right (18):
Gene therapy is a rapidly growing field in medicine which is also of inestimable clinical potential. Gene therapy has many potential uses in treating disease and has been reviewed extensively. See, e.g., Boggs, Int. J. Cell Cloning. (1990) 8:80-96, Kohn et al, Cancer Invest. (1989) 7 (2):179-192, Lehn, Bone Marrow Transp. (1990) 5:287-293, and Verma, Scientific Amer. (1990) pp. 68-84. Genetically transformed human stem cells have wide potential application in clinical medicine, as agents of gene therapy.

Brief Summary Paragraph Right (19):
Gene therapy describes an emerging approach to clinical treatment which has evolved from earlier approaches in medical care. The earliest approaches to medical care, evolving over centuries, included gross surgical procedures and the administration of crude mixtures as medicinal agents. In the past century, biochemical pharmacology has supervened as the major method of medical treatment. Under this paradigm, pure biochemical molecules are delivered to the patient. In general, such pharmacologic agents act either as poisons (such as antimicrobials or cancer chemotherapy agents), physiologic mimetics which stimulate endogenous receptors (e.g., opiates, adrenergic agonists), or physiologic antagonists which block endogenous receptors (e.g. antihypertensives, anaesthetics).

Brief Summary Paragraph Right (20):
Gene therapy is, by definition, the insertion of genes into cells for the purpose of medicinal therapy. The principle underlying gene therapy is to, rather than deliver doses of pharmacologic molecules, deliver a functional gene whose RNA or protein product will produce the desired biochemical effect in the target cell or tissue. There are several potential advantages of gene therapy over classical biochemical pharmacology. First, inserted genes can produce extremely complex molecules, including RNA and protein, which can be extraordinarily difficult or impossible to administer and deliver themselves. Next, controlled insertion of the desired gene into specific target cells can control the production of gene product to defined tissues. Finally, gene therapy can in principle be permanent within an individual, as the gene will continue to function in the target cells and their progeny.

Brief Summary Paragraph Right (21):
There are several problems that must therefore be addressed for successful gene therapy. The first is to be able to insert the desired therapeutic gene into the chosen cells. Second, the gene must be adequately expressed in the target cell, resulting in the appropriate levels of gene product. Finally the RNA or protein produced must be properly processed by the target cell so that it is functional, i.e. so that gene therapy actually infers clinical therapy. Several methods of gene insertion into human cells in vitro are listed in Table 1.

Brief Summary Paragraph Right (22):
Other techniques, such as homologous recombination, are being developed as well in many laboratories. Research in gene therapy has been on-going for several years in several types of cells in vitro, progressed to animal studies, and has recently entered the first human clinical trial(s).

Brief Summary Paragraph Right (23):
The hematopoietic system is an ideal choice as a delivery system for gene therapy. Hematopoietic cells are readily accessible, simply by bone marrow aspiration or by peripheral blood mononuclear cell harvest. Once the genetic insertion is accomplished in vitro the treated cells can be reinfused intravenously, after which the genetically transformed cells will home to and develop in the bone marrow. Since mature blood cells circulate throughout the body, the genetically modified cells can deliver the specific gene product to any desired tissue.

Brief Summary Paragraph Right (25):
Successful hematopoietic stem cell gene therapy has broad application, to both diseases specific to the hematopoietic system and to other organ system diseases. Within the hematopoietic system, both inherited and acquired diseases can be treated by stem cell gene therapy. For example, hemoglobin deficiencies such as .alpha. and .beta. Thalessemias could be treated by the insertion of the gene coding for the globin .alpha. or .beta. chain, together with regulatory sequences that confer high level tissue specific erythrocytes (see, Grosveld et al, Cell (1987) 51:975-986). Similarly, sickle cell anemia could be corrected by the genetic insertion of the fetal globin gene into hematopoietic stem cells, as the regulated expression of high levels of fetal hemoglobin are sufficient to prevent sickling in red cells despite the copresence of sickle hemoglobin (see, Sunshine et al, J. Molec. Biol. (1979) 133:435).

Brief Summary Paragraph Right (27):
The particular suitability of hematopoietic stem cell gene therapy for the replacement of congenitally deficient gene products is particularly evident in the treatment of lymphocyte immunodeficiency diseases, such as severe combined immunodeficiency due to adenosine deaminase deficiency. Retroviral gene therapy of circulating T cells with the ADA gene has been found to be successful at reducing the clinical immunodeficiency experienced by these patients, but the effects are only temporary because the transfected T lymphocytes have a finite life span in vivo (see, Kasid et al, Proc. Nat. Acad. Sci. (USA) (1990) 87:473-477, or Culver et al Proc. Nat. Acad. Sci. (USA), (1991) 88:3155-3159). If, however, the gene could be successfully transfected into hematopoietic stem cells, then all of the T cells which arose from these stem cells would contain and express the ADA gene. Therefore, since the transfected stem cells would persist and proliferate for the life of the patient, the T cell ADA deficiency would be permanently treated by a single gene transfer stem cell treatment (see, Wilson et al, Proc. Natl. Acad. Sci., (U.S.A.) (1990) 87:439-443).

Brief Summary Paragraph Right (28):
In addition to treating inherited enzymatic abnormalities of the hematopoietic system, stem cell gene therapy could be useful for protecting stem cells and their progeny from toxic exogenous agents such as viruses or chemotherapy. For example, gene transfer of DNA sequences encoding the TAR binding site of the HIV TAT transactivating factor have been shown to protect T cells from spreading infection by the HIV virus (see, Sullenger et al, Cell (1990) 63:601-608). Stable transaction of these sequences into hematopoietic stem cells would result in a pool of T cells, all arising from these stem cells, which were relatively or absolutely resistant to the spread of HIV.

Brief Summary Paragraph Right (30):
One can readily envision that hematopoietic stem cell gene therapy will also be useful for acquired hematopoietic disease such as leukemia, lymphoma and aplastic anemia. Once the genetic causes of these diseases is discovered, insertion of a gene whose product either overcomes that of the abnormal gene in the cell or corrects it directly (perhaps by splicing out and replacing the gene) would correct the abnormality.

Brief Summary Paragraph Right (31):
On a broader level, however, hematopoietic stem cell gene therapy can be useful for the treatment of diseases outside the hematopoietic system as well. Gene transfer of DNA sequences carrying therapeutic soluble proteins could give rise to mature blood cells which permanently secreted the desired amounts of a therapeutic molecule. By

way of examples, this approach could be useful for the treatment of, e.g., diabetes mellitus by the insertion of DNA sequences for insulin along with regulatory DNA sequences that controlled the proper expression of the transfected insulin gene, perhaps in response to elevated plasma glucose levels. Systemic hypertension could be treated by genetic insertion of stem cells with DNA sequences encoding secretory peptides which act as competitive inhibitors to angiotensin converting enzyme, to vascular smooth muscle calcium channels, or to adrenergic receptors. Alzheimer's disease could possibly be treated by. genetic insertion into stem cells of DNA sequences encoding enzymes which break down amyloid plaques within the central nervous system.

Brief Summary Paragraph Right (32):
The many applications of gene therapy, particularly via stem cell genetic insertion, are thus well known and have been extensively reviewed (see, Boggs et al, supra, Kohn et al, supra, Lehn, supra, and/or Verma et al, supra). There are indeed increasing examples of some success in achieving therapeutic gene transfer into differentiated human stem cells, as described for example in T lymphocytes (see, Kalsd et al, Proc. Nat. Acad. Sci. (U.S.A.), (1990) 87:473-477, Culver et al, Proc. Nat. Acad. Sci. (U.S.A.) (1991) 88:3155-3159).

Brief Summary Paragraph Right (34):
The major impediment to achieving successful human hematopoietic stem cell gene therapy has been the inability to insert genes into human hematopoietic cells under conditions in which the stem cells are dividing and proliferating. Successful stable gene insertion into a target cell requires that the target cell undergo at least one round of cell division. Thus if stem cells are not dividing in the presence of the desired genetic material, the material will not be stably inserted into the stem cells. Prior to the development of the present invention, no system existed which supported the ex vivo division and proliferation of human stem and no successful genetic transformation of human stem cells has been possible.

Brief Summary Paragraph Right (35):
There is therefore a considerable need for methods and compositions for the ex vivo replication and stable genetic transformation of human Stem cells and for the optimization of human hematopoietic progenitor cell cultures, particularly in light of the great potential for stem cell expansion, progenitor cell expansion, and gene therapy offered by these systems. Unfortunately, to date, attempts to achieve such results have been disappointing.

CLAIMS:

23. The ex vivo human hematopoietic or stromal stem cell composition of claim 2, wherein said composition comprises at least one member selected from the group consisting of human peripheral blood mononuclear cells, human bone marrow cells, human fetal liver cells, and human cord blood cells.

24. The ex vivo human hematopoietic or stromal stem cell composition of claim 23, wherein said human peripheral blood mononuclear cells, human bone marrow cells, human fetal liver cells, and human cord blood cells, are enriched for said human hematopoietic or stromal stem cells.

25. The ex vivo human hematopoietic or stromal stem cell composition of claim 2 wherein said composition comprises at least one member selected from the group consisting of human peripheral blood mononuclear cells, human bone marrow cells, human fetal liver cells, and human cord blood cells; said composition also comprising human stromal cells.

44. The ex vivo human bone marrow stem cell composition of claim 3, comprising stable genetically transformed human hematopoietic or stromal lineage cells.

results in dog studies are reasonably predictive of efficacy in human patients.

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L5: Entry 8 of 80 File: USPT Dec 4, 2001

DOCUMENT-IDENTIFIER: US 6326198 B1
TITLE: Methods and compositions for the ex vivo replication of stem cells, for the optimization of hematopoietic progenitor cell cultures, and for increasing the metabolism, GM-CSF secretion and/or IL-6 secretion of human stromal cells

Brief Summary Paragraph Right (11):
The lack of stable progenitor cell and mature blood cell production in these cultures has led to the belief that they are unable to support continual stem cell renewal and expansion. It has therefore been presumed that the cultures either lack a critical stem cell stimulant(s) and/or contain a novel stem cell inhibitor(s). But while explanations for failure to detect HGFs and uninduced stromal cell cultures have been suggested, the null hypothesis, which combines the failure to detect HGFs and the relative failure of human liquid marrow cultures, would be that the culture systems used in vitro do not provide the full range of hematopoietic supportive function of adherent bone marrow stromal cells in vivo.

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L5: Entry 10 of 80 File: USPT Jul 31, 2001

DOCUMENT-IDENTIFIER: US 6268213 B1
TITLE: Adeno-associated virus vector and cis-acting regulatory and promoter elements capable of expressing at least one gene and method of using same for gene therapy

Detailed Description Paragraph Right (96):
In vitro cultures assays of hematopoiesis in FAC patients have consistently shown a reduction or absence of colony forming progenitor cells (CFU-C) of all hematopoietic lineages (Sanders and Freeman 1978, Br. J. Haematol. 40:277-287; Alter, et al., 1992, Blood 80:3000-3008). Long-term bone marrow culture experiments, which require the development of an adherent stromal cell layer for the maintenance of progenitor growth, have also revealed a significant reduction in the number of CFU-C (Stark, et al., 1992, Br. J. Haematol, 83:554-559). Although defects of the bone marrow stromal elements cannot be totally excluded, fibroblasts (a major cell constituent of the stroma) from FA patients seem to express the appropriate repertoire of hematopoietic growth factors (Bagby, et al., 1993, Exp. Haematol, 21-1419-1426). Available evidence suggests, therefore, that FA is a disorder of a primitive hematopoietic stem cell. We have been able to show that CD34.sup.+ progenitors from a FA(C) patient retain the hypersensitivity to MMC which characterized cultured FA cells.

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L5: Entry 17 of 80 File: USPT Dec 5, 2000

DOCUMENT-IDENTIFIER: US 6156301 A
TITLE: Use of interleukin-7 to stimulate proliferation of hematopoietic cell precursors

Detailed Description Paragraph Right (64):
Adherent bone marrow stromal cells were transfected with the plasmid pSV3neo containing the SV40 T antigen transforming sequences using a calcium phosphate procedure as described by Southern et al., J. Mol. Appl. Genet. 1:327 (1982), and Graham et al., Virology 52:456 (1973); as modified by Wigler et al., Cell 14:725 (1978). The transfected adherent cells were removed with trypsin:EDTA and cloned by limiting dilution. The supernatants from the resultant clones were tested for IL-7 activity and the best producer (I.times.N/A6) was expanded for further study. This cell line was monitored on a monthly basis for mycoplasma using commercially-available mycoplasma detection kits.

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L5: Entry 18 of 80 File: USPT Sep 26, 2000

DOCUMENT-IDENTIFIER: US 6123915 A
TITLE: Methods for using agents that bind to VCAM-1

Detailed Description Paragraph Right (31):
Thirteen years ago, Dr. Michael Dexter and his colleagues (65) established the methodology for maintaining the survival and development of primitive bone marrow stem cells over long periods of time in vitro. This so-called long-term bone marrow culture (LTBMC) system, while initially optimized for the growth of murine cells, has subsequently been modified to support the growth of human bone marrow (66). The essential feature of both systems is the development of an adherent layer of mesenchymal cells derived from the stromal cell population of the bone marrow. The inductive influences provided by the stromal elements of these cultures are essential for the growth and self-renewal and the differentiation of stem cells in these cultures to more specialized progeny (e.g., myeloid progenitors) in a manner which reflects the in vivo situation. Both cytokines released by the stromal cells and adhesive interactions between stromal cells and hemopoietic precursors are important in this process (67, 68). At this point, many of the specific adhesive mechanisms utilized in this in vitro system and its in vivo counterpart are ill-defined.

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L5: Entry 20 of 80 File: USPT Jul 11, 2000

DOCUMENT-IDENTIFIER: US 6087113 A
TITLE: Monoclonal antibodies for human mesenchymal stem cells

Brief Summary Paragraph Right (26):
In a further aspect, the present invention is directed to a method for repairing skeletal defects. The method comprises the steps of providing a bone marrow specimen containing mesenchymal stem or progenitor cells, adding cells from the bone marrow specimen to a medium (i.e. "complete medium") which contains factors that stimulate mesenchymal stem or progenitor cell growth without differentiation and allows, when cultured, for the selective adherence of only the mesenchymal stem or progenitor cells to a substrate surface, culturing the bone marrow-medium mixture, removing the non-adherent matter from the substrate surface by replacing the medium with a fresh medium of the same composition, and, allowing the isolated adherent mesenchymal stem or progenitor cells to culturally expand. The culturally expanded mesenchymal stem or progenitor cells are then applied to a porous carrier, such as a porous calcium phosphate and/or hydroxyapatite ceramic block, which is subsequently implanted into the defective skeletal tissue. It has been found that through the use of the porous carrier containing the mesenchymal stem or progenitor cells, these mesenchymal cells fairly rapidly differentiate into bone producing cells. As a result, the method and device of the invention are an effective means for treating skeletal and other connective tissue disorders.

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L5: Entry 20 of 80 File: USPT Jul 11, 2000

US-PAT-NO: 6087113
DOCUMENT-IDENTIFIER: US 6087113 A

TITLE: Monoclonal antibodies for human mesenchymal stem cells

DATE-ISSUED: July 11, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Caplan; Arnold I.	Cleveland Heights	OH		
Haynesworth; Stephen E.	Cleveland Heights	OH		

US-CL-CURRENT: 435/7.1; 435/7.2, 435/7.21, 530/388.2, 530/388.7

CLAIMS:

What is claimed is:

1. A process for recovering human mesenchymal stem cells from a cell mixture derived from human bone marrow comprising contacting the cell mixture with a monoclonal antibody which selectively binds to an antigen on human mesenchymal stem cells and recovering antibody bound cells from said cell mixture.

2. A process for separating a cell population containing human mesenchymal stem cells from a cell mixture derived from human bone marrow comprising contacting the cell mixture with a monoclonal antibody which selectively binds to an antigen on human mesenchymal stem cells and separating antibody bound cells from said cell mixture.

3. The process of claim 1 wherein said human mesenchymal stem cells are isolated, purified, culture-expanded human mesenchymal stem cells.

4. The process of claim 2 wherein said human mesenchymal stem cells are isolated, purified, culture-expanded human mesenchymal stem cells.

5. A method for determining the presence of human mesenchymal stem cells in a cell mixture derived from human bone marrow, comprising:

contacting the cell mixture with a monoclonal antibody that selectively binds human mesenchymal stem cells; and

detecting the presence of said antibody.

6. The method of claim 5 wherein said human mesenchymal stem cells are culture-expanded.

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L5: Entry 24 of 80 File: USPT Oct 26, 1999

DOCUMENT-IDENTIFIER: US 5972703 A
TITLE: Bone precursor cells: compositions and methods

Brief Summary Paragraph Right (19):
In another aspect, stromal cells present in bone marrow cells can be removed by exposing bone marrow cells to an adherent surface, typically tissue culture plastic or glass.

Detailed Description Paragraph Right (5):
In another aspect, the population of bone precursor cells can be enriched by removing stromal cells present in bone marrow cells. Removal of stromal cells can be accomplished by exposing bone marrow cells to an adherent surface, typically tissue culture plastic or glass. Stromal cells adhere to tissue culture plastic or glass while bone precursor cells do not. Stromal cells can be removed before or after the immune purification step. Preferably, stromal cells are removed prior to the immune purification step. The use of solid surfaces such as tissue culture plastic or glass is well known in the art. Tissue culture plastic and glass can be treated (e.g. silicone, nitrocellulose, nickel, etc.) to promote or inhibit cell adhesion. Treated and untreated surfaces are available commercially.

CLAIMS:

3. The process of claim 1 further comprising removing adherent stromal cells by exposing said popuation of bone marrow cells to an adherent surface.

25. The enriched population of bone precursor cells of claim 23 further comprising removing adherent stromal cells by exposing said poplation of bone marrow cells to an adherent surface.

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Search Results - Record(s) 1 through 3 of 3 returned.

☐ 1. Document ID: US 6387663 B1

L15: Entry 1 of 3 File: USPT May 14, 2002

US-PAT-NO: 6387663
DOCUMENT-IDENTIFIER: US 6387663 B1

TITLE: Targeting pharmaceutical agents to injured tissues

DATE-ISSUED: May 14, 2002

US-CL-CURRENT: 435/69.7; 424/1.69, 424/520, 424/9.4, 424/93.7, 435/174, 435/180, 435/252.3, 435/366, 435/395, 435/4, 435/69.1, 530/350, 530/402

APPL-NO: 9/ 127134
DATE FILED: July 31, 1998

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 2. Document ID: WO 9724144 A1, AU 9647435 A

L15: Entry 2 of 3 File: DWPI Jul 10, 1997

DERWENT-ACC-NO: 1997-363458
DERWENT-WEEK: 199733

TITLE: Preparation of bone marrow stromal cells - by culturing, transfection with exogenous gene and cryo-preservation, for use in gene therapy

PRIORITY-DATA: 1995WO-US16991 (December 29, 1995)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 9724144 A1	July 10, 1997	E	045	A61K048/00
AU 9647435 A	July 28, 1997		000	A61K048/00

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
WO 9724144A1	December 29, 1995	1995WO-US16991	
AU 9647435A	December 29, 1995	1995WO-US16991	
AU 9647435A	December 29, 1995	1996AU-0047435	
AU 9647435A		WO 9724144	Based on

INT-CL (IPC): A61 K 48/00

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 3. Document ID: US 6019965 A, WO 9523862 A1, AU 9462558 A, EP 791061 A1, JP 09509828 W, US 5777193 A, AU 704486 B

L15: Entry 3 of 3 File: DWPI Feb 1, 2000

DERWENT-ACC-NO: 1995-320577
DERWENT-WEEK: 200013

TITLE: Transgenic mouse carrying a disrupted colony stimulating factor gene - used to identify treatative agents for and in the gene therapy of alveolar proteinosis using the granulocyte macrophage colony stimulating factor gene

PRIORITY-DATA: 1994WO-AU00103 (March 4, 1994), 1998US-0044960 (March 20, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 6019965 A	February 1, 2000		000	A61K038/19
WO 9523862 A1	September 8, 1995	E	078	C12N015/27
AU 9462558 A	September 18, 1995		000	C12N015/27
EP 791061 A1	August 27, 1997	E	000	C12N015/27
JP 09509828 W	October 7, 1997		102	A01K067/027
US 5777193 A	July 7, 1998		000	A61K049/00
AU 704486 B	April 22, 1999		000	C12N015/27

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
US 6019965A	October 24, 1994	1994US-0211651	Div ex
US 6019965A	March 20, 1998	1998US-0044960	
US 6019965A		US 5777193	Div ex
WO 9523862A1	March 4, 1994	1994WO-AU00103	
AU 9462558A	March 4, 1994	1994AU-0062558	
AU 9462558A	March 4, 1994	1994WO-AU00103	
AU 9462558A		WO 9523862	Based on
EP 791061A1	March 4, 1994	1994EP-0909877	
EP 791061A1	March 4, 1994	1994WO-AU00103	
EP 791061A1		WO 9523862	Based on
JP 09509828W	March 4, 1994	1994WO-AU00103	
JP 09509828W	March 4, 1994	1995JP-0522566	
JP 09509828W		WO 9523862	Based on
US 5777193A	March 4, 1994	1994WO-AU00103	
US 5777193A	October 24, 1994	1994US-0211651	
US 5777193A		WO 9523862	Based on
AU 704486B	March 4, 1994	1994AU-0062558	
AU 704486B		AU 9462558	Previous Publ.
AU 704486B		WO 9523862	Based on

INT-CL (IPC): A01 K 67/027; A61 K 9/08; A61 K 9/12; A61 K 9/72; A61 K 35/14; A61 K 35/42; A61 K 37/02; A61 K 38/00; A61 K 38/19; A61 K 48/00; A61 K 49/00; C07 G 15/00; C07 K 14/435; C07 K 14/535; C07 K 15/06; C12 N 5/00; C12 N 15/09; C12 N 15/11; C12 N 15/27; C12 Q 1/00; C12 Q 1/68

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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L16: Entry 7 of 39 File: USPT Dec 4, 2001

DOCUMENT-IDENTIFIER: US 6326198 B1
TITLE: Methods and compositions for the ex vivo replication of stem cells, for the optimization of hematopoietic progenitor cell cultures, and for increasing the metabolism, GM-CSF secretion and/or IL-6 secretion of human stromal cells

Brief Summary Paragraph Right (18):
Gene therapy is a rapidly growing field in medicine which is also of inestimable clinical potential. Gene therapy is, by definition, the insertion of genes into cells for the purpose of medicinal therapy. Research in gene therapy has been on-going for several years in several types of cells in vitro and in animal studies, and has recently entered the first human clinical trials. Gene therapy has many potential uses in treating disease and has been reviewed extensively. See, e.g., Boggs, Int. J. Cell Cloning. (1990) 8:80-96, Kohn et al, Cancer Invest. (1989) 7 (2):179-192, Lehn, Bone Marrow Transp. (1990) 5:287-293, and Verma, Scientific Amer. (1990) pp. 68-84.

Brief Summary Paragraph Right (19):
The human hematopoietic system is an ideal choice for gene therapy in that hematopoietic stem cells are readily accessible for treatment (bone marrow or peripheral blood harvest), they are believed to posses unlimited self-renewal capabilities (inferring lifetime therapy), and upon reinfusion, can expand and repopulate the marrow. Unfortunately, achieving therapeutic levels of gene transfer into stem cells has yet to be accomplished in humans.

Brief Summary Paragraph Right (21):
A salient problem which remain to be addressed for successful human gene therapy is the ability to insert the desired therapeutic gene into the chosen cells in a quantity such that it will be beneficial to the patient. To date, no method for doing this is available.

Brief Summary Paragraph Right (22):
There is therefore a considerable need for methods and compositions for the ex vivo replication of human stem cells and for the optimization of human hematopoietic progenitor cell cultures, particularly in light of the great potential for stem cell expansion, progenitor cell expansion, and gene therapy offered by these systems. Unfortunately, to date, attempts to achieve such results have been disappointing.

CLAIMS:

1. A method for obtaining ex vivo human stem cell division comprising culturing human hematopoietic stem cells contained in a human bone marrow composition in a liquid culture medium in the presence of human bone marrow stromal cells to obtain ex vivo human stem cell division therein, wherein the culture medium is replaced, either continuously or periodically, at a rate of about 1 ml of medium per ml of culture per about 24 to about 48 hour period.

17. A method for expanding a human hematopoietic stem cell pool, comprising culturing a human bone marrow composition comprising said human stem cell pool in a liquid culture medium in the presence of human bone marrow stromal ells to obtain ex vivo human stem cell expansion therein, and removing metabolic product and replenishing depleted nutrients while maintaining said culture under physiologically acceptable conditions, wherein the culture medium is replaced, either continuously

or periodically, at a rate of about 1 ml of medium per ml of culture per about 24 to about 48 hour period.

33. A method for culturing human hematopoietic progenitor cells comprising culturing a human bone marrow composition comprising said human hematopoietic progenitor cells in a human liquid hematopoietic culture medium in the presence of human bone marrow stromal cells to obtain ex vivo human progenitor cell division therein and removing metabolic products and replenishing depleted nutrients while maintaining said culture under physiologically acceptable conditions, wherein the culture medium is replaced, either continuously or periodically, at a rate of about 1 ml of medium per ml of culture per about 24 to about 48 hour period.

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DOCUMENT-IDENTIFIER: US 6238908 B1
TITLE: Apparatus and method for maintaining and growth biological cells

Brief Summary Paragraph Right (6):
In parallel with this advancement, and largely dependent upon its success, are the numerous gene therapy approaches being advanced to initial clinical trials that involve the ex vivo genetic manipulation of cells and tissue. Gene therapy involves transduction of the genome of the cell to achieve correction of a defective gene, regulation of a disease condition, or production of a beneficial molecule. Those gene therapy procedures that will benefit from ex vivo administration of a gene vector to an expanded or donor tissue in order to enhance the targeting of the gene and avoid this systemic administration (likely to include most conceivable gene therapies for the next decade or longer) will be well served by the above advancements in tissue genesis and production.

Brief Summary Paragraph Right (9):
Although lacking the physical geometry that is a feature of other tissues or organs, bone marrow is a tissue comprised of many different cell types, ranging from different stromal fibroblasts, mesenchymal cells, to stem cells and the other cells of the hematopoietic system. The ex vivo process found to be needed for ex vivo bone marrow growth, was to mimic the natural functional environment of the bone marrow, providing for the controlled nutrient perfusion and oxygenation of the stem and stromal cell components under precise conditions of temperature and medium composition. Key to the success was to provide culture conditions that were concurrently amenable for each of the many different cell types that are found in human bone marrow.